Involvement of different second messengers in parathyroid hormone- and interleukin-1-induced interleukin-6 and interleukin-11 production in human bone marrow stromal cells.

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Previous studies have suggested that increased secretion of bone active cytokines, such as interleukin-6 (IL-6) and interleukin-11 (IL-11), from osteoblasts and stromal cells play a pivotal role in the activation of osteoclasts and the genesis of osteoporosis. Various systemic and local factors can stimulate IL-6/IL-11 production, but the intracellular mechanism for such stimulation is largely unknown. In this study, we characterized the second messenger signaling in parathyroid hormone (PTH)- and IL-1-induced production of IL-6/IL-11 and studied the possible modulating effects of estrogen. rhPTH(1-34) and rhIL-1 alpha dose-dependently stimulated IL-6 and IL-11 production from human bone marrow stromal cells (hBMSCs). Agonists for protein kinase A (PKA) (forskolin), and protein kinase C (PKC) (phorbol 12-myristate 13-acetate; PMA) also stimulated IL-6/IL-11 production. Rp-diastereoisomer of adenosine cyclic 3',5'-phosphorothioate (Rp-cAMPS) and H-8, inhibitors of PKA, significantly inhibited PTH-stimulated IL-6/IL-11 production, but did not inhibit IL-1-stimulated IL-6/IL-11 production. In contrast, staurosporine and calphostin C, inhibitors of PKC, suppressed IL-1-stimulated, but not PTH-stimulated, IL-6/ IL-11 production. Pretreatment of cells with 17 beta-estradiol (17 beta-E2) antagonized IL-1-stimulated IL-6 production. However, PTH-stimulated IL-6 production and IL-1- and PTH-stimulated IL-11 production were not affected by 17 beta-E2. Similarly, 17 beta-E2 inhibited PMA-stimulated IL-6 production, whereas neither forskolin-stimulated IL-6/ IL-11 production nor PMA-stimulated IL-11 production was affected by 17 beta-E2. These results indicate that different second messengers are involved in PTH- and IL-1-induced IL-6 and IL-11 production by hBMSCs: PTH and IL-1 stimulate IL-6/IL-11 production via a PKA-dependent and PKC-dependent pathway, respectively. Furthermore, our results suggest that regulation of cytokine production by estrogen in hBMSCs is selective; only the IL-1-induced IL-6 production, which is mediated by PKC pathway, is inhibited, but PTH-induced IL-6 production and PTH/IL-1-induced

IL-11 production are not inhibited by estrogen.

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